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Whether High-Intensity Statins Actually Reduce Mortality from COVID-19 Needs to be Evaluated in Appropriate Studies

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Abstract
In a retrospective study of 26 445 COVID-19 patients by Ho *et al*, it was found that the odds of in-hospital mortality decreased by 24% in patients receiving high-dose statin therapy (atorvastatin 40-80 mg/d, rosuvastatin 20-40 mg/d) compared to patients not receiving statin therapy. It was concluded that the use of high-intensity statins in acute COVID-19 may confer a mortality benefit. However, the study has several limitations that put the results and their interpretation into perspective. Whether high-intensity statins actually reduce mortality in COVID-19 patients needs to be evaluated through prospective, multicenter, double-blind, placebo-controlled crossover studies.

Keywords: Statins, SARS-CoV-2, COVID-19, Mortality, Outcome

Letter to the Editor
We read with interest the article by Ho *et al*. about a retrospective, multicenter study with stored data from 26 445 COVID-19 patients, which were stratified depending on home statin or no statin use, high- intensity (atorvastatin 40-80 mg/d, rosuvastatin 20-40 mg/d) or low-to-moderate intensity statin use (all other statins), and their impact on in-hospital mortality [1]. When these data were analyzed using a linear model and logistic regression to predict odds ratios, in-hospital mortality decreased in patients receiving high-dose statis as compared to patients not receiving statins [1]. It was concluded that high-intensity statins may be beneficial in acute COVID-19 [1]. The strengths of the study are the large number of patients included (N = 26 445), using effective stratification criteria, such as home statin or no statin use and high-intensity versus moderate-intensity statin use, and the inclusion of various comorbidities with regard to their influence on in-hospital mortality [1]. However, some points require further discussion.

The first point is that mortality does not usually depend on just 1 factor. COVID-19 patients are often multimorbid, suggesting that several other outcome measures may influence mortality. These other factors should be included in the logistic regression to assess which cofactors influence mortality in addition to statin therapy.

The second point is that COVID-19 patients may die not just from cardiovascular involvement, but rather from pulmonary disease, immunological disease, superinfections or sepsis. These are not positively influenced by statins.

The third point is that it is not specified how many of the included patients were already receiving statin therapy before admission and how many were receiving statins for the first time during hospitalization. Separating these 2 groups is essential because side effects or beneficial effects may depend on the duration of statin treatment. People who have been taking statins for several years often have additional vascular risk factors, such as obesity, hyperlipidemia, hypertension, and coronary artery disease, which increase their risk of COVID-19-related mortality. This contradicts the study's finding that COVID-19-related mortality decreases in people receiving statins.

The fourth point is that comedication was not included in the assessment. Since COVID-19 treatment is usually polypragmatic and most patients suffer from comorbidities, it is very likely that most of the included patients were taking not only statins but also other medications. Since the metabolism of statins largely depends on competition with other drugs at each step, it is important to know which other drugs were administered to assess the extent to which they influenced statin serum levels.

A fifth point is that it was not reported how many of the included patients suffered side effects from high-intensity statin therapy. Since statins are not free from side effects [2], it is imperative to know how many of them suffered from myalgia, creatine-kinase elevation, or even rhabdomyolysis. Statins can be complicated by rhabdomyolysis, especially when combined with other drugs, such as direct-acting antivirals, antimicrobials (eg macrolid antibiotics), and glucocorticoids [3]. Since

rhabdomyolysis can have a negative impact on renal functions [4], we should be informed how many of the included patients experienced statin-induced rhabdomyolysis. Rhabdomyolysis occurs particularly in patients with myopathy [5], so it would also be worthwhile to know how many of the included patients had myopathy. In fact, we should know how any statin-related side effects may affect the final result of the study.

Limitations of the study were that it was restricted to HCA Healthcare hospitals, and the studies with controversial results were not discussed in detail [6]. The study also did not take into account the fact that statins also increase the angiotensin-converting enzyme 2 receptors on the cell surface to facilitate SARS-CoV-2 entry, which in turn may increase SARS-CoV-2 infection and mortality rates, as opposed to being hypothesized to reduce them.

In summary, the limitations of this interesting study reveal the need to put the results and their interpretation into perspective. Clarifying these weaknesses would strengthen the conclusions and could improve the study. The question of whether high-intensity statins actually reduce mortality in COVID-19 patients must be comprehensively investigated in the future. Such studies should use a prospective, double-blind, placebo-controlled crossover design and also analyze possible side effects of statin therapy.

Declarations

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Consent to Participation: Not applicable.

Consent for Publication: Not applicable.

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Author Contribution: JF was responsible for the design and conception, discussed available data with coauthors, wrote the first draft, and gave final approval.

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