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LETTER TO THE EDITOR

Is Heterogeneity in the Effects of Statins on Infection Outcomes across Clinical Studies Due to Bias?

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We read with great interest the review about the usefulness of statins as antimicrobials published by Hennessy et al. (1). We agree that future prospective studies focusing on statin and pathogen specificities are warranted. However, we would like to add some additional considerations for future studies that could explain the substantial variation between clinical studies.

While the results from *in vitro* and animal models are generally promising, improved infection outcomes in clinical settings are mainly observed when patients are pretreated with statins and generally not with *de novo* statin use (1).

Focusing on patients that are already using statins prior to follow-up (prevalent users) may introduce biases that can be largely prevented by focusing on *de novo* statin users (incident users), including treatment selection bias and adjustment for covariates affected by prior treatment (2–4). For example, a meta-analysis evaluating the effect of statins on cardiovascular disease found that the greater the proportion of prevalent statin users in observational studies, the larger the discrepancy with estimates from randomized controlled trials (4).

Differences in patient populations may be another important underlying cause of the substantial variation between clinical studies. For example, in a recent study focusing on incident statin users, we observed that statins were associated with a reduced risk of infection among patients with type II diabetes (5). In contrast, statins had hardly any effect among patients without diabetes (5). The results of animal and *in vitro* studies suggest that statins may be more effective against infections among diabetic patients than among patients without diabetes, by reducing Rac1 activation and/or inhibiting biofilm formation (5–9). Moreover, among patients without diabetes, the potentially smaller benefits may be outweighed by the increased risk of incident diabetes among statin users (5, 10).

In a *post hoc* analysis of a randomized controlled trial, pravastatin was associated with a similar reduced risk of recurrent urinary tract infections among adults with persistent microalbuminuria, another condition associated with elevated Rac1 activation (11). The observations that this protective effect was also seen for urinary tract infections, a condition in which a reduced inflammatory response is not necessarily beneficial, and was stronger for recurrent urinary tract infections (11) suggest that a reduction in bacterial invasion may play a more important role than anti-inflammatory effects.

In conclusion, besides the suggestions provided by the authors of this extensive review (1), we want to stress the importance of restricting the analysis to statin initiators instead of prevalent users. When the follow-up is long enough and potential informative censoring is taken into account by, for example, inverse probability of censoring weighting (2), one could also validly assess the potential impact of longer use of statins prior to infection. In addition, future prospective studies should consider potential effect modification by comorbidities such as diabetes.

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